REMARKS

Claim 1 has been amended. Support for the amendment can be found on page 13 lines 1-5 of the Specification as filed. No new matter has been introduced herewith. As a result of the Amendment, claims 1-8, 10, 12-22, 34 and 36-38 are presented for examination. The following addresses the substance of the Office Action.

Claim Rejections under 35 U.S.C. §103

The Examiner has rejected Claims 1-8, 10, 12-15, 17-22, 34, and 36-38 under 35 U.S.C. §103(a) over Peterson et al. (WO 95/30026) in view of Lokhart et al. (USP 5,770,722). More specifically, the Examiner alleges that it is *prima facie* obvious that selection of the specific number of spots and therefore naturally the concentration of DNA per square cm in an array and a spacer of specific length represent routine optimization, that is not considered inventive, lacking evidence from the inventors to the contrary. Furthermore, the Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Peterson et al., wherein each spot contains double-stranded DNA sequences for the binding of transcriptional factors and the double-stranded DNA sequences are connected to the surface of the solid support, with the spacer of Lockhart et al. The Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the PTO must cite one or more references that provide some suggestion or motivation to modify the references to achieve the claimed invention, provide a reasonable expectation of success to achieve the claimed invention, and finally, the cited art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Here, the cited art either taken alone or in combination, fails to provide any of the required factors.

Peterson et al. describes assays for screening for drugs which interfere with sequence-specific protein-DNA binding. Peterson et al. neither suggest nor mention the use of a spacer. Peterson does have, on average, 10 bp in front of the transcription factor binding site. However, Peterson does not disclose or suggests spacers between about 50 and about 250 bp as recited in the claims as amended herein. Furthermore, the methods of Peterson are performed on multiwell plates as opposed to the microarrays utilized in the present methods. The 10 bp sequences disclosed in Peterson are insufficient for use in the context of microarrays.

Spacers between about 50 bp and about 250 bp provide advantages in binding efficiency (See Figure 5). Enhanced binding efficiency is important, particularly in the context of microarrays where the binding of multiple factors to their recognition sites may be simultaneously assessed on a single array. Because the binding conditions would be uniform on the array, it is likely that the binding conditions (salt concentrations, temperature, etc.) would be less than optimal for each of transcription factors. In view of the suboptimal binding conditions, the spacer provides important advantages in detecting and quantifying transcription factor binding. Spacers of the recited lengths provide significant increases in signal levels.

The short 10 bp sequences of Peterson et al. do not provide the significant enhancement of signal levels obtained with spacers of the recited lengths. In addition, the transcriptional factor which is detected in Peterson's method is added intentionally at a known concentration to the reaction mixture. This further highlights the difference in present invention and the method of Peterson et al.: the present invention permits detection of transcription factors present in a cell or cell lysate, while the methods of Peterson use transcription factors added at known concentrations to identify compounds which modulate binding of the factors to their recognition sites.

Lockhart et al. (US 5,770,722) teach a method of forming a plurality of diverse unimolecular, double-stranded oligonucleotides on a solid support. In the method of Lockhart et al. the two oligonucleotides that constitute the double-stranded (ds) DNA sequence are synthesized independently and are preferably generated by light-directed synthesis. In contrast, in some embodiments, the present invention may be used with PCR-amplified dsDNAs which provide advantages as: 1) the resulting strands are 100% complementary, a prerequisite for the binding of transcriptional factors as mutations are hardly tolerated and lead to a binding inhibition; 2) the dsDNA molecules generated by PCR are not limited in size. On the contrary, the *in situ* synthesis used in Lockhart et al. presents limitations regarding the size and fidelity of oligonucleotides that can be generated. This is why Lockhart et al. use oligonucleotides which are "about 6 to about 30 nucleotides in length and exhibit complementarity of from 90 to 100%" (p.10, l. 33-37). These characteristics are, however, very limiting when working with transcriptional factor binding.

The method of Lockhart et al. involves the optional use of a spacer which "can be any of a variety of molecules which are inert to the subsequent conditions for polymer synthesis" (p 9,

lines 19-21). This excludes the use of dsDNA as a spacer, as dsDNA molecules would not be inert for further polymer synthesis. Indeed, deprotecting the dsDNA would enable a dual synthesis, starting from both free DNA ends. Moreover, if a spacer of between about 50 and about 250 bp, as recited in the present claims, were used in the method of Lockhart et al., this would imply the synthesis of long DNA molecules with the spacer and the transcriptional factor binding site. This, however, represents the major limitation inherent to *in situ* oligonucleotide synthesis, and is the main reason why Lockhart et al. limit their method to the preferred use of oligonucleotides which are 6 to 30 nucleotides in length.

Therefore, Peterson et al., and Lockhart et al. references fail to support a *prima facie* case of obviousness. These references both fail because neither provides the requisite motivation to combine, reasonable expectation of success, or teaches all the limitations of the claimed invention. Because of these deficiencies, Applicants submit that the PTO has failed to articulate a *prima facie* case of obviousness, and as such, the present rejection of Claims 1-8, 10, 12-15, 17-22, 34, and 36-38 under 35 U.S.C. 103 should be withdrawn.

The Examiner has rejected Claim 16 under 35 U.S.C. §1039(a) over Peterson et al. (WO 95/30026) in view of Lockhart et al. (USP 5,770,722) and further in view of Voytas et al (USP 5,976,795). More specifically, the Examiner alleges that because Voytas et al. teach the method wherein the transcriptional factor is the HIV integrase, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Peterson et al., wherein each spot contains double-stranded DNA sequences for the binding of transcriptional factors and the double-stranded DNA sequences are connected to the surface of the solid support, with the spacer of Lockhart et al. and the transcriptional factor of Voytas et al.. The Applicants respectfully disagree.

The field of the invention of Voytas et al. (US 5,976,795) is molecular biology, particularly in the area of retrotransposons. The Voytas invention provides retrotransposons and retrotransposon derivatives and methods for their uses. Specifically, it provides Ty5-6p and derivatives. Ty5-6p and its derivatives integrate preferentially in the genome of eukaryotes in silent chromatin and in regions like silent chromatin. Ty5-6p insertions can be used to regulate the life span of cells, to genetically mark cells, to deliver gene therapy and to identify genes involved in development and in senescence. This field is not related to the present invention nor to Peterson et al. in view of Lockhart et al.

The term "HIV integrase" is only disclosed at one location (column 2, lines 1-12). It is not even the HIV integrase transcription factor which is mentioned but the Ini1 protein which is a homologue of the yeast transcription factor SNF5. They only mention that Ini1 specifically interacts with HIV integrase. This document does neither disclose nor suggest a method for the detection of the HIV integrase which could be combined with Peterson et al. in view of Lockhart et al.

Therefore, a skilled person would not be motivated to combine Peterson et al., Lockhart et al. and Voytas et al. to reach the present invention.

The Peterson et al., Lockhart et al. and Voytas et al. references fail to support a *prima facie* case of obviousness. These references all fail because neither provides the requisite motivation to combine, reasonable expectation of success, or teaches all the limitations of the claimed invention. Because of these deficiencies, Applicants submit that the PTO has failed to articulate a *prima facie* case of obviousness, and as such, the present rejection of Claim 16 under 35 U.S.C. 103 should be withdrawn.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are inapplicable to the present claims. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned at (805) 547-85586 (direct line), to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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